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Disseminated Intravascular Coagulation: Clinical and Laboratory Aspects

Michael J. Carey[1] and George M. Rodgers[1,2,3,4]*

[1]Department of Pathology, University of Utah Health Sciences Center, Salt Lake City, Utah
[2]Department of Medicine, University of Utah Health Sciences Center, Salt Lake City, Utah
[3]Veterans Administration Medical Center, Salt Lake City, Utah
[4]ARUP Laboratories, Salt Lake City, Utah

Disseminated intravascular coagulation (DIC) is a complex acquired coagulopathy resulting from excessive thrombin formation. Abnormal tissue factor (TF) expression is a major mechanism initiating DIC in many disorders, including obstetrical complications, sepsis, cancer, and trauma. Numerous laboratory tests are available to monitor DIC, but most patients are adequately managed using only routine hemostasis screening tests, and assays for fibrinogen and D-dimer. Treatment of DIC should focus on reversing the underlying disorder initiating the coagulopathy. Novel treatments are being investigated for treating DIC; many of these experimental modalities target the excessive TF activity that characterizes DIC. Am. J. Hematol. 59:65–73, 1998. © 1998 Wiley-Liss, Inc.

Key words: DIC; hemostasis; bleeding disorders; tissue factor

INTRODUCTION

Disseminated intravascular coagulation (DIC) is an acquired coagulation disorder that occurs when the normal hemostatic balance is disturbed, primarily by excessive thrombin formation. Thrombin generation is normally tightly regulated by the natural anticoagulant mechanisms, antithrombin III and the protein C pathway, as well as the fibrinolytic mechanism that restores vessel patency after formation of the hemostatic plug [1]. Tissue factor pathway inhibitor (TFPI) also inhibits coagulation by binding to a complex of TF/factor VIIa/factor Xa [2]. Other mechanisms that regulate thrombin formation include the mononuclear-phagocyte system that removes soluble tissue factor (TF) and soluble complexes of fibrin monomer, and hepatocytes that clear activated coagulation proteases and tissue-plasminogen activator from the circulation. The normal liver also synthesizes the components of the natural coagulant pathways. Figure 1 illustrates mechanisms that maintain the hemostatic balance and regulate thrombin formation.

Etiologies of DIC are summarized in Table I; these disorders are all characterized by excessive generation of thrombin and plasmin. Figure 2 summarizes major pathologic mechanisms that contribute to the coagulopathy of DIC, emphasizing the importance of abnormal tissue factor expression.

ALTERATIONS OF HEMOSTASIS IN DIC

This complex hemostatic system is vulnerable to dysregulation. If endothelial cell function is compromised and unable to contain the expanding wave of coagulation by the natural anticoagulant mechanisms, hemostatic control is lost and DIC develops [3].

Disruption of the endothelium leads to exposure of smooth muscle cell and fibroblast tissue factor activity. This may occur with obstetrical accidents (placental abruption) or severe trauma. Tissue factor is a transmembrane protein cofactor constitutively expressed by certain cells, such as fibroblasts. The tissue factor-factor VII_a complex can rapidly initiate coagulation by activation of factors IX and X. Tissue factor activity is abundant in brain, lung, and placenta, and can also be induced by endothelial cells and monocytes in response to cytokines such as interleukin-1 (IL-1) and tumor necrosis factor, or by endotoxin [1,4]. In contrast, cultured endothelial cells stimulated with cytokines or endotoxin upregulate tissue

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*Correspondence to: Dr. George M. Rodgers, Division of Hematology-Oncology, University of Utah Health Sciences Center, Salt Lake City, UT 84132.

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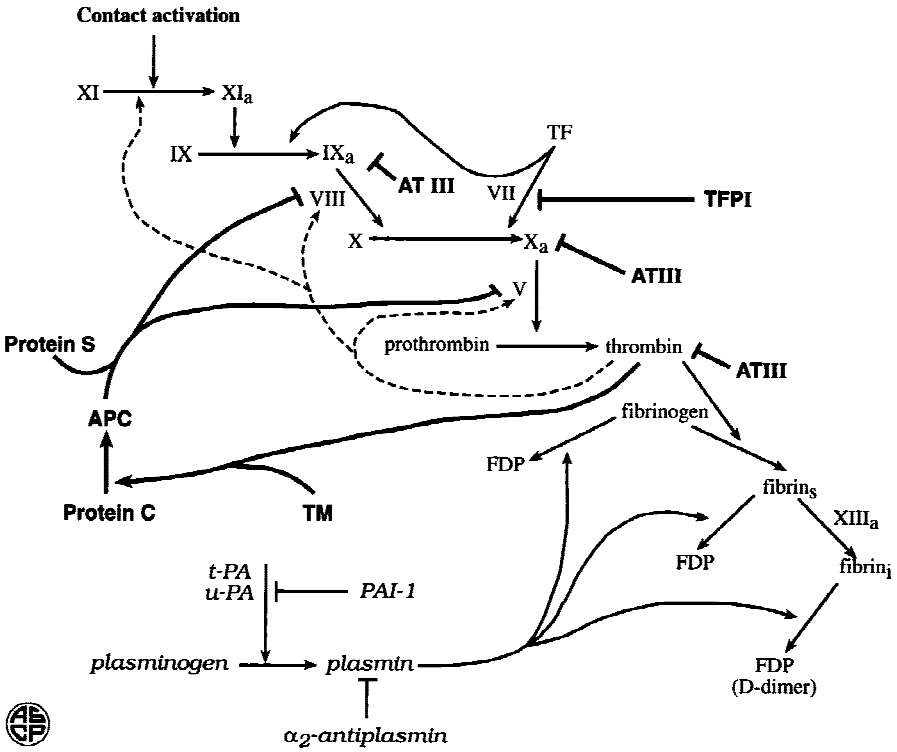

Fig. 1. Regulation of coagulation and fibrinolysis. The interactions between the coagulation and fibrinolytic mechanisms afford numerous opportunities for dysfunction resulting in DIC. The fibrinolytic system is depicted in italics, and the regulatory anticoagulant pathways are shown in bold. The dotted line represents a positive feedback loop depicting thrombin activation of factors V, VIII, and XI. Tissue factor (TF) expression is the major initiator of coagulation in DIC. Anticoagulant mechanisms (antithrombin III, AT III; tissue factor pathway inhibitor, TFPI; protein C pathway [thrombomodulin, TM; activated protein C, APC] regulate the extent of thrombin formation. The fibrinolytic mechanism generates plasmin to digest fibrin thrombi, but in DIC, excessive fibrinolysis may occur. t-PA = tissue-plasminogen activator; u-PA = urokinase-plasminogen activator; PA1-1 = plasminogen activator inhibitor-1; $fibrin_s$ = soluble (non-crosslinked) fibrin; $fibrin_i$ = insoluble (crosslinked) fibrin; FDP = fibrin(ogen) degradation products. From Carey MJ, Rodgers GM: DIC. Check—Sample Clinical Hematology (CH 98-3), ASCP Press, with permission.

TABLE I. Etiologies of Disseminated Intravascular Coagulation

Obstetrical complications
Placental abruption, septic abortion
Infections
Bacterial, rickettsial, viral
Cancer
Adenocarcinoma, promyelocytic leukemia
Hematologic (non-malignant)
Intravascular hemolysis (transfusion reactions)
Vascular disorders
Aneurysms, hemangiomas, vasculitis
Trauma
Burns, brain injury
Miscellaneous
Snakebite, prothrombin complex concentrates, graft rejection, homozygous protein C deficiency

factor pathway inhibitor (TFPI) only slightly. This disparity between TF and its inhibitor induced by inflammatory mediators of sepsis results in a procoagulant phenotype, which may lead to DIC. Whether TF can be expressed by in vivo vascular endothelium is controversial. However, some investigators have reported vascular endothelial cell TF expression by immunohistochemical methods [5,6]. Cytokines upregulate expression of tissue factor while simultaneously downregulating thrombomodulin expression [1]. Abnormal promyelocytes in acute promyelocytic leukemia may release tissue factor contained in granules into the circulation to initiate coagulation [7]. Many tumor cells, especially adenocarcinomas, constitutively express tissue factor on their surface (Fig. 2) [8].

In DIC, generation of large amounts of thrombin, combined with dysfunction of control mechanisms, may result in fibrin deposition in the microvasculature, leading to tissue ischemia. Depletion of platelets, fibrinogen, prothrombin, and the other hemostatic proteins may lead to a consumption coagulopathy, and, if severe enough, bleeding. Plasminogen activators are secreted as an endothelial cell response to thrombosis to initiate fibrinolysis (secondary fibrinolysis) [1]. In DIC, fibrinolysis is excessive, such that α_2-antiplasmin is consumed, and free plasmin circulates. Free plasmin degrades both fibrinogen and fibrin, leading to degradation products (FDP) that interfere with platelet aggregation, fibrin polymerization, and thrombin activity, further potentiating the risk of bleeding. Consequently, the clinical presentation of DIC may show evidence of predominant thrombotic symptoms, or fibrinolysis with hemorrhage, or both. Microangiopathic hemolytic anemia may result as red blood cells are sheared by intravascular fibrin strands; however, many patients with DIC will not exhibit red cell fragmentation [9].

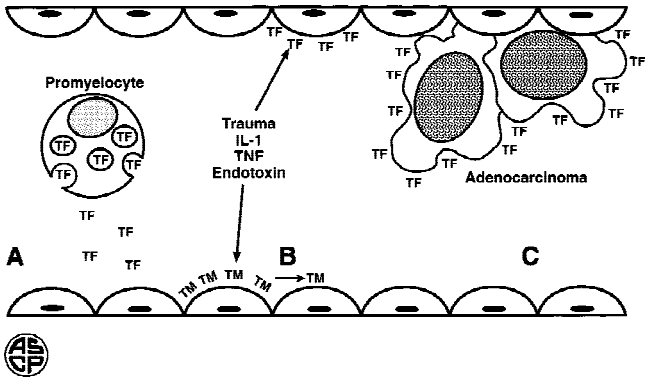

Fig. 2. Etiologies of DIC associated with excess tissue factor expression. A: Promyelocytic leukemia cells may release tissue factor contained in granules into the circulation. B: Endothelial cell disruption may lead to increased expression of vessel wall tissue factor activity. Cytokines and endotoxin induce endothelial cells and monocytes to upregulate expression of tissue factor activity, while downregulating the expression of thrombomodulin activity. C: Adenocarcinoma tumor cells may constitutively express tissue factor activity on their surface. TF, tissue factor; TM, thrombomodulin. From Carey MJ, Rodgers GM: DIC. Check—Sample Clinical Hematology (CH 98-3), ASCP Press, with permission.

Role of Cytokines

Although there are numerous etiologies for DIC (Table I), a common pathway for activation of coagulation by these disorders is release of various cytokines [10]. The expression of endotoxin (lipopolysaccharide) by the external membrane of gram-negative bacteria can trigger an inflammatory response, hypotension, DIC, and, ultimately, end-organ failure. DIC occurs as mediators are released from macrophages, monocytes, and endothelial cells to perturb coagulation and fibrinolysis. Endotoxin interaction with the target cell is mediated through the CD14 receptor, or by CD14-independent mechanisms, resulting in cytokine secretion [11].

The symptoms of septic shock (fever, hypotension, DIC, myocardial depression) are mediated by cytokines, including IL-1 [12], IL-6, IL-8, platelet activating factor, and TNF_{α} [12]. Elevation of IL-8 levels is correlated with high mortality in sepsis and with the presence of DIC [13]. IL-1 and TNF enhance endothelial cell TF expression in vitro and in vivo [1]; these cytokines also decrease thrombomodulin activity [1] and increase vascular expression of E-selectin, a leukocyte adhesion molecule that enables activated neutrophils to adhere to endothelium. Levels of E-selectin are increased in the plasma of patients with DIC, probably reflecting endothelial cell activation by cytokines [14].

Certain disorders associated with DIC may also disable hemostatic control mechanisms in various ways. For example, hepatic disease may compromise synthetic and clearance functions that are important in maintaining the balance between coagulation and anticoagulation. Patients with leukemia will have abnormal marrow function and an insufficient thrombopoietic response to thrombocytopenia.

DIC needs to be distinguished from other coagulopathies associated with bleeding, including vitamin K deficiency and the uncommon disorder, primary fibrinolysis. In both vitamin K deficiency and primary fibrinolysis, evidence for excessive thrombin generation is absent (no thrombocytopenia or increased D-dimer levels, see below), and clinical evidence for vitamin K deficiency (antibiotic therapy, malnutrition, liver disease) or primary fibrinolysis (genitourinary malignancy) is present.

LABORATORY TESTING FOR DIC

The laboratory diagnosis of DIC is difficult because many laboratory tests lack sensitivity and specificity. A 1989 report evaluated platelet count, FDP by latex agglutination, D-dimer by latex agglutination, fibrinogen concentration, and thrombin time in a prospective study of patients with DIC [15]. Elevated levels of FDP and D-dimer had a positive predictive value of 100% [15]. D-dimer is a specific test for fibrin degradation, while the FDP test is positive if either fibrinogen or fibrin is degraded by plasmin. Other studies place the sensitivity of the D-dimer test at 94%, with a specificity of 80% [16]. A low platelet count lacks specificity, as it may be due to an underlying disease, such as sepsis, or medications. Many patients with DIC do not present with hypofibrinogenemia, and patients with chronic DIC may have normal fibrinogen levels, because fibrinogen is an acute-phase reactant.

Recent recommendations by others suggest documentation of four events to establish a laboratory diagnosis of DIC: (1) Procoagulant activation is characterized by an increase in blood levels of prothrombin fragment 1 and 2, fibrinopeptides A and B, thrombin-antithrombin (TAT) complex, and soluble fibrin (representing fibrin that has not been crosslinked by factor XIIIa), and decreased platelet count; (2) Fibrinolytic activation is characterized by an increase in blood levels of D-dimer, FDP, plasmin-α_2-antiplasmin (PAP) complex, and soluble fibrin; (3) Inhibitor consumption is characterized by an increase in blood levels of TAT complex and PAP complex, and a decrease in blood levels of AT-III and α_2-antiplasmin activity; (4) End-organ injury or failure is characterized by an increase in serum lactic dehydrogenase and creatinine levels, and a decrease in blood pH and pO_2 levels [17,18]. Several of these tests are extraneous, or are not offered commercially. Documentation of these events may be of esoteric interest, but it is not generally recommended for routine diagnosis of DIC.

Liver disease, vitamin K deficiency, warfarin intoxication, and primary fibrinolysis may be associated with

prolonged PT and PTT values, and patients with liver disease may also have thrombocytopenia, hypofibrinogenemia, and elevations in FDP levels. A key diagnostic test to distinguish DIC from the other coagulopathies is the D-dimer test, which should only be elevated in DIC. Patients with liver disease who have an elevated D-dimer will also have an additional disorder, usually infection or cancer, to account for the positive D-dimer test [19]. False-positive D-dimer results (as measured by latex agglutination) can be seen in patients with rheumatoid factors (IgM). A quantitative D-dimer ELISA test is available and does not have this false-positive disadvantage. For those laboratories that do not have D-dimer ELISA instrumentation, a protamine sulfate precipitation test can be done to determine whether a patient with a positive D-dimer test and rheumatoid factor has DIC or not. Factor VIII coagulant activity may be low in DIC and is usually normal or elevated in liver disease.

OTHER LABORATORY MARKERS FOR DIC

Tissue factor is a key initiator of coagulation in DIC. Thus, plasma antigen levels of tissue factor (TF) may reflect the development of DIC [20]. A Japanese study demonstrated elevated tissue factor (TF) and tissue factor pathway inhibitor (TFPI) concentrations in patients with DIC at presentation. If TFPI levels decreased during DIC, then they might prove valuable as a means of monitoring treatment progress. Elevated TF levels were found predominantly in patients with DIC caused by cancer and leukemia, while TFPI was elevated in all underlying disease categories. Plasma TFPI concentrations did not correlate with plasma TF, or other hemostatic markers of DIC such as FDP and fibrinogen. Plasma TFPI levels did not decrease, and actually increased in the majority of patients with DIC; thus TFPI levels are not useful as a disease marker [21].

Measurements of increased plasma soluble fibrin monomer (SFM) or protamine sulfate titration may be useful for monitoring the anticoagulant treatment of DIC. It has also been suggested that plasma SFM may be a useful clinical marker for the diagnosis of pre-DIC and DIC. Pre-DIC refers to the retrospective diagnosis of patients who were treated before actual DIC became manifest. The plasma SFM test is time-consuming, however, and its utility in the patient care setting is questionable [22]. This test is also less sensitive than other tests, such as D-dimer.

In some cases, thrombocytopenia may be due to bone marrow involvement, resulting in decreased platelet production. Glycocalicin is released after plasmin degradation of platelet membrane glycoprotein (GP)Ibα, a component of the GPIb/IX complex. Increased platelet destruction in DIC patients is reflected by increased glycocalicin concentrations. Determination of plasma glycocalicin concentrations may help distinguish thrombocytopenia due to platelet consumption from that due to bone marrow insufficiency [23]. Techniques to measure ''platelet reticulocytes'' (RNA-containing platelets) or serum thrombopoietin levels may also distinguish destructive from aplastic thrombocytopenia.

Platelet activating factor (PAF) is a chemical mediator of acute inflammatory diseases produced by neutrophils, endothelial and other cells. Clinical studies have shown elevated levels of PAF and endotoxin in septic DIC, and found an inverse relationship between levels of PAF and platelet counts in these patients [24]. Hemostatic studies on patients 1 week before the onset of DIC have shown elevated levels of TAT complex and PAP complex when compared with non-DIC patients [25].

PRACTICAL ASPECTS OF LABORATORY DIAGNOSIS AND MONITORING OF DIC

In clinical practice, a DIC panel typically consists of a platelet count, fibrinogen level, prothrombin and partial thromboplastin times (alone and with correction by mixing with normal plasma), and a measurement of D-dimer (or FDP) levels. Examination of a blood film may reveal red cell fragmentation. Laboratory studies directed toward identifying the underlying disease should also be undertaken (blood cultures, etc.). As outlined above, many additional tests are available to diagnose and follow DIC patients. However, little practical information is gained from these assays, and most laboratories will not routinely offer them. The DIC panel suggested is useful not only for diagnosis of the disorder, but is also helpful in determining response to therapy, and need for replacement therapy. Cessation of DIC results in decreased D-dimer (or FDP) levels and a rise in plasma fibrinogen levels.

TREATMENT OF DIC

It is important to emphasize that primary therapy of DIC should be focused on reversing the underlying disease process that has initiated activation of coagulation.

A discussion of the treatment aspects of DIC is complex because numerous underlying disease processes produce DIC, and specific treatments for each disorder are necessary. For example, DIC associated with abruptio placentae is best treated by evacuation of the uterus, while DIC due to gram-negative infection is properly addressed by antibiotic therapy. This section will focus on general recommendations to correct bleeding and thrombotic complications of DIC independent of treatment targeted to the underlying disease. Additional disease-specific recommendations for various forms of DIC have been recently summarized [26]. This section will also discuss novel therapies that may be available soon to

specifically inhibit coagulation mechanisms responsible for DIC. If patients exhibit none of the clinical complications of DIC (bleeding, thrombosis, microangiopathic hemolysis, shock), no additional therapy is warranted.

Correction of the Coagulopathy

A significant complication of DIC is bleeding, due to consumption of coagulation proteins and platelets, as well as elevated levels of FDP that inhibit platelet function [27] and fibrin polymerization [28]. While correction of the latter (FDP) defect requires interruption of the pathologic process generating thrombin (and subsequently, FDP), the consumption coagulopathy of DIC can be improved with blood products—cryoprecipitate to replete fibrinogen, and platelets to reverse thrombocytopenia. Fresh-frozen plasma can also be utilized to correct a persistent coagulopathy in patients who bleed despite correction of hypofibrinogenemia and thrombocytopenia. It may not be necessary to prophylactically use blood products to correct the laboratory coagulopathy in patients who are not bleeding, and in whom DIC is being appropriately treated by reversing the underlying disease [29].

Each unit of cryoprecipitate contains ~250 mg of fibrinogen [30]. It is desirable to maintain the fibrinogen level of bleeding DIC patients at 100–150 mg/dl. For an average-sized adult (70 kg) with a plasma volume of ~3,000 ml and a fibrinogen level of 50 mg/dl, administration of 1.5 g fibrinogen (6 U of cryoprecipitate) should raise the fibrinogen level to 100 mg/dl. Sterile fibrinogen concentrates are not yet available for routine use in the United States. Some patients who previously received lyophilized fibrinogen concentrates have developed thromboembolic complications [31].

Patients with active DIC who are bleeding and who have platelet counts less than 50,000/μl should be considered for platelet transfusion. Unlike patients with thrombocytopenia due to marrow failure in whom platelet transfusions may be deferred until the 10,000–20,000/μl threshold level is reached, DIC patients will usually have high levels of FDP that inhibit platelet function, and may also have an acquired storage pool defect due to thrombin activation. Therefore, DIC patients will probably require a higher platelet count level for adequate hemostasis.

Controversial Therapies

Anticoagulants. The use of anticoagulants such as heparin has been studied in DIC with mixed results. The best results of heparin therapy have been reported in the subset of patients with chronic DIC of malignancy (Trousseau's syndrome) in whom dramatic inhibition of thromboembolism occurs with therapeutic heparin [8,32]. Of note, up to 30% of these patients who respond to heparin therapy will have recurrent thrombosis on warfarin therapy, necessitating prolonged treatment of these patients either with therapeutic heparin or low-molecular-weight heparin [8,32]. In patients with DIC due to prostate cancer, ketoconazole [33] or anti-androgen therapy [34] may also be helpful.

Heparin therapy has also been recommended for certain patients who have DIC associated with acute leukemia, especially promyelocytic leukemia [35]. Heparin therapy at 500 U/hr is suggested for those patients in whom it is difficult to maintain fibrinogen levels over 100 mg/dl or who have rising FDP levels [35]. This patient group may also benefit from anti-fibrinolytic therapy (discussed below). Finally, the availability of all-*trans*-retinoic acid, a differentiation therapy for promyelocytic leukemia, may obviate the need for heparin therapy [36].

In patients with typical (acute) DIC due to sepsis, placental abruption, etc., the utility of heparin is much less clear [37–39]. Although some investigators have published guidelines for heparin use in acute DIC [37,40], in practice, most physicians are reluctant to use heparin in this group of patients; heparin therapy is primarily reserved for patients with chronic DIC and thromboembolism.

Antifibrinolytic drugs. Epsilon-aminocaproic acid and tranexamic acid prevent bleeding by inhibiting fibrin dissolution. One important use of anti-fibrinolytic drugs is in patients with primary fibrin(ogen)olysis who have no evidence for persistent thrombin formation. Unfortunately, in patients with DIC and secondary fibrinolysis, the use of these drugs may lead to serious thromboembolic complications [41]. There are certain instances in which these drugs may be useful in DIC patients, such as in promyelocytic leukemia with a significant fibrinogenolytic component [35]. These drugs should only be used in conjunction with heparin, or in patients in whom it is documented that DIC is absent.

Antithrombin III (ATIII). Since many patients with DIC will have low levels of ATIII due to consumption, and since ATIII replacement theoretically should inhibit initiation of coagulation and ameliorate DIC, numerous studies have investigated the utility of ATIII in patients with DIC [reviewed in ref. 42]. Although ATIII concentrates can normalize plasma ATIII levels in DIC patients, a survival benefit has not been clearly demonstrated [42]. However, a recent animal study of sepsis-induced DIC indicated that administration of massive amounts of ATIII (to achieve plasma ATIII levels ≥300% of normal) reduced mortality and morbidity in the model [43]. The addition of low-molecular-weight heparin therapy to animals who also received high-dose ATIII did not enhance the beneficial effects of ATIII and resulted in bleeding complications. These results suggest that pharmacologic concentrations of ATIII may exert a beneficial effect by mechanisms other than that currently under-

TABLE II. Novel Therapies for DIC*

Classification of therapy	Mechanism	Status	References
Protease inhibitors			
Aprotinin	Inhibits fibrinolysis (kallikrein, plasmin)	Animal studies	47
		Used in humans to reduce surgical bleeding	48,49
Gabexate	Inhibits multiple proteases (thrombin, factor X_a, plasmin, kallikrein)	Human studies	45,46
α_1-antitrypsin-Pittsburgh	Inhibits thrombin and factors XI_a, XII_a, and kallikrein	Animal studies	50–52
ATIII	Inhibits multiple proteases	Human studies	42–45
TF inhibitors			
Monoclonal antibodies	Inhibits TF activity	Animal studies	53–55
TFPI	Inhibits TF activity and binds to endotoxin	Animal studies (human studies in progress)	57,58 56
Dithiocarbamates	Inhibits TF gene transcription	Animal studies	59,62
Miscellaneous			
Pentoxifylline	Inhibits ''immediate-early'' gene activation (TNF, IL-6, TF)	Animal studies	54
Activated protein C	Promotes anticoagulation by inactivation of factors V_a and $VIII_a$	Animal studies	65
Thrombomodulin	Promotes anticoagulation by inactivation of factors V_a and $VIII_a$	Animal studies	66
PAF antagonist	Prevents endotoxin-induced increase in TNF levels	Animal studies	67

*DIC, disseminated intravascular coagulation; AT, antithrombin; TF, tissue factor; TFPI, tissue factor pathway inhibitor; TNF, tumor necrosis factor; PAF, platelet activating factor.

stood [43]. High-dose ATIII was also reportedly useful in ameliorating organ failure in a small pediatric case series with DIC [44].

Novel Therapies

Identification of critical mechanisms in initiation or progression of DIC has led to studies of new agents in modifying DIC in animal models and in humans. Table II summarizes many of these novel therapies, their mechanisms of action, and their status (animal studies vs. human trials). As indicated, few agents have yet been tested in human DIC trials.

Gabexate has been studied extensively in Japan. In an uncontrolled trial of gabexate therapy in DIC patients (mostly associated with malignancy), gabexate was as effective as heparin therapy [45]. A large multicenter Japanese study found that gabexate also improves clinical symptoms and hemostasis parameters in DIC patients [46]. However, clear demonstration of a survival advantage with gabexate has not yet been reported.

Another protease inhibitor, aprotinin, has been investigated in an animal model of DIC [47]. Although aprotinin has been used successfully to reduce blood loss during cardiac surgical procedures [48], its use has also been associated with widespread thrombosis, especially in patients receiving lower heparin doses [49]. These results suggest that if aprotinin is to be considered for use in human DIC, it will be important to use this drug in conjunction with adequate heparin dosage, similar to what is suggested for the anti-fibrinolytic drugs.

Recombinant α_1-antitrypsin-Pittsburgh is a potent mutant protease inhibitor of thrombin and certain contact coagulation factors (XI_a, kallikrein, factor XII_a). This product has been shown to have activity in animal models of DIC [50–52].

The importance of TF activity in initiating DIC in sepsis has led to animal studies that established the efficacy of antibodies to TF [53–56] or TFPI [57,58] in reducing the mortality of sepsis.

Two types of recombinant TFPI are being investigated for efficacy in DIC: the full-length TFPI molecule and a modified two-domain TFPI molecule [56]. Both forms of TFPI have been demonstrated to be effective in animal models of sepsis and DIC. In a primate model, recombinant full-length TFPI decreased mortality as well as IL-6 levels [57]. A phase 2 investigation of recombinant TFPI in sepsis and DIC is underway [56]. This drug appears to be safe from the standpoint of bleeding complications.

A new therapeutic focus of DIC is that of inhibition of TF gene transcription. The NF-κB pathway is a key transcriptional mechanism in induction of TF activity. The importance of this pathway in human DIC was shown in a recent report in which persistent binding of NF-κB in mobility shift assays was seen in non-surviving patients with acute sepsis [59]. Surviving patients exhibited decreased NF-κB binding [59]. These data suggest that interruption of the NF-κB mechanism, at least transiently, might be clinically useful in DIC.

One class of drugs that specifically inhibits the NF-κB pathway is dithiocarbamates [60]. These drugs inhibit TF induction in vitro [61] and in an animal model of DIC [62]. Dithiocarbamates have been used in humans to treat other disorders [63,64], and are candidate drugs to treat human DIC.

Anticoagulant components of the protein C pathway (activated protein C [65], thrombomodulin [66]) have been studied in animal models of sepsis-induced DIC. Abrogating or enhancing the protein C pathway in vivo has been demonstrated to dramatically alter the outcome

of sepsis in animal models of DIC [65]. As listed in Table II, therapies targeted to cytokine secretion or receptors are also being investigated.

There are advantages and disadvantages to each of these potential therapies. Recombinant proteins such as TFPI and α_1-antitrypsin Pittsburgh, and monoclonal antibodies to TF will be relatively expensive. Additionally, the efficacy of most of the drugs listed in Table II has only been demonstrated when they have been given prior to induction of experimental DIC. Notable exceptions to this statement include ATIII [42–44], gabexate [45,46], TFPI [56–58], and dithiocarbamates [62], which have been shown to ameliorate DIC in humans or experimental models after initiation of DIC.

Current Treatment Recommendations

Many patients with DIC will require no therapy other than treatment of their underlying disorder. Patients with Trousseau's syndrome will benefit from therapeutic heparin or low-molecular-weight heparin, but few will require blood products. Those patients with acute DIC, consumption coagulopathy (hypofibrinogenemia, significant thrombocytopenia), and bleeding will require cryoprecipitate and platelets. If the coagulopathy and bleeding persists despite replacement of fibrinogen and platelets, fresh-frozen plasma infusion may be helpful. Most patients with acute DIC will not benefit from heparin therapy. Antifibrinolytic drugs should be reserved for DIC patients with a significant fibrinolytic component (e.g., promyelocytic leukemia), and should be used in conjunction with heparin therapy. Of the newer treatments under investigation, ATIII is the most widely available; however, ATIII will be very expensive, and controlled studies demonstrating decreased mortality with its use have not been reported. The potential utility of the novel therapies listed in Table II remains unproven for human DIC, but recombinant TFPI is promising and is currently under study in human trials. The role of the novel agents in treating DIC is uncertain, but they may be most useful in the patients who have a reversible underlying illness and who have not had a prompt response to appropriate standard therapy (e.g., a patient with sepsis-associated DIC who has not responded to antibiotic therapy).

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